

disposal is markedly reduced in patients with type 2 diabetes (Shen *et al.*, 1970; Ginsberg *et al.*, 1975; Reaven, 1983). The main tissues that increase the rate of glucose uptake in response to an increase in plasma insulin levels are skeletal muscle and adipose tissue (Kruszynska and Olefsky, 1996). Skeletal muscle is the major site of glucose disposal (Defronzo *et al.*, 1985), and consensus opinion suggests that in the majority of patients with type 2 diabetes, there is a defect in insulin-stimulated glucose disposal by skeletal muscle.

Many prospective studies of populations at high risk for type 2 diabetes (Lillioja *et al.*, 1993; Taylor *et al.*, 1994), and nondiabetic first degree relatives of patients with type 2 diabetes (Eriksson *et al.*, 1989; Warram *et al.*, 1990) have suggested that in most patients, the initial inherited lesion is insulin resistance. Thus, genetic factors are thought to have an important role in the development of diabetes. Recently, a putative diabetes gene was localized in the *NIDDM1* region of chromosome 2. This putative diabetes-susceptibility gene encodes an ubiquitously expressed member of the calpain-like cysteine protease family, calpain 10 (CAPN10) (Horikawa *et al.*, 2000).

Insulin resistance leads to a compensatory hyperinsulinemia, which is sufficient to maintain normal glucose tolerance, or at least impaired glucose tolerance. It is widely believed that with time, this compensatory mechanism becomes defective in a subset of patients due to  $\beta$ -cell failure, and leads to overt type 2 diabetes (Kruszynska and Olefsky, 1996; Bailey, 1999).

Tissue glucose uptake is mediated by a family of five glucose transporters that have a tissue-specific distribution. One of them, GLUT4, is very responsive to an acute rise in insulin levels. GLUT4 is expressed only in skeletal muscle, adipocytes, and heart muscle (Shepherd *et al.*, 1993). Insulin stimulates glucose transport by recruiting GLUT4-containing vesicles from the intracellular pool to the plasma membrane, and may also increase GLUT4 intrinsic activity (Shepherd *et al.*, 1993; Guma *et al.*, 1995; Kelley *et al.*, 1996). The impairment of whole-body glucose utilization in type 2 diabetes is associated with defects in insulin-stimulated glucose transport in skeletal muscle

(Bonadonna *et al.*, 1993; Kelley *et al.*, 1996), and adipocytes (Kashiwagi *et al.*, 1983; Garvey *et al.*, 1991).

Insulin resistance is independently associated with obesity, which accompanies 80% of patients with type 2 diabetes in the West (Kruszynska and Olefsky, 1996; Ferrannini, 1998). In addition, insulin resistance is more severe in obese patients with type 2 diabetes (Seely, 1993).

## B. Ginseng

The ginseng root has been used for over 2000 years, in the belief that it is a panacea and promotes longevity. As described in Chinese traditional medicine textbooks, its effectiveness reaches mythical proportions (Lee, 1992; Huang, 1999). Seven major species of ginseng are distributed in East Asia, Central Asia, and North America (Huang, 1999). Most studies of ginseng have utilized constituents from common species including: *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng), and *Panax japonicus* (Japanese ginseng). However, the constituents from any of the species of ginseng currently known or discovered in the future would be expected to have utility.

Active constituents found in most ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids (Lee, 1992). Ginsenosides are classified as steroidal saponins. There is a wide variation (2-20%) in the ginsenoside content of different species of ginseng (Huang, 1999). Moreover, pharmacological differences within a single species cultivated in two different locations have been reported. For example, the potency of extracts from *Panax quinquefolius*, cultivated in the U.S.A., for modulating neuronal activity is significantly higher than for the same species cultivated in China (Yuan, 1998b).

The dried root of *Panax ginseng* is a highly valued herb in the Far East, and has gained popularity in the West during the last decade. Previous investigations demonstrated that ginseng root possesses multiple pharmacological activities (Lee, 1992; Gillis, 1997; Yuan *et al.*, 1998a, 1998b, 1999a; Huang, 1999). The two common species

of ginseng are *Panax ginseng* (Asian ginseng), and *Panax quinquefolius* (American ginseng). To date, it is the root of ginseng that is well known as a herbal medicine. Commercially available ginseng extracts and powders are manufactured from the ginseng root, and previous studies have shown effects of the root (Kimura *et al.*, 1981a; 1981b; Kimura and Suzuki 1981; Bensky and Gamble, 1993; Huang, 1999; Kimura *et al.*, 1999).

### 1. *In vitro studies*

Kimura (1980) reported that a partially-purified fraction of ginseng root enhanced glucose-stimulated insulin release from pancreatic islet cells of KK-CAY mice, which exhibits type 2 diabetes. In alloxan-diabetes mice, Kimura *et al.*, (1981a) showed that a water soluble fraction of ginseng root increased glucose-stimulated insulin release. Okuda and Yoshida (1980) reported that when adipose tissue of rats was incubated with an acidic peptide extracted from ginseng root, ACTH and growth hormone-induced lipolysis was inhibited, and lipogenesis was stimulated. Other studies have reported that an extract of ginseng root and the ginsenoside Rb2 increased ATP levels in hepatic tissue of streptozotocin-induced diabetic rats (Yokozawa *et al.*, 1991; Yokozawa and Oura, 1991). Ginsenoside Rb2 also increased albumin mRNA in the liver of streptozotocin-induced diabetic rats (Yokozawa *et al.*, 1996). These studies did not provide any insight into the mechanisms of action of ginseng root.

### 2. *In vivo studies*

Several studies have reported that a water extract of *Panax ginseng* root lowered fasting blood glucose levels in alloxan-induced diabetic mice (Kimura *et al.*, 1981a; Kimura *et al.*, 1999). In another study, Kimura *et al.*, (1981b) showed that the glucose-lowering effect of a ginseng root extract fraction, in alloxan-induced diabetic mice, was abolished by antibodies to bovine insulin. In streptozotocin-induced diabetic rats, ginsenoside Rb2 caused a significant decrease in blood glucose levels, and regulated hepatic enzymes that maintain blood glucose within the physiological range (Yokozawa *et al.*, 1985). Kimura and Suzuki (1981) reported that a fraction of ginseng root extract improved glucose tolerance in genetically diabetic KK-CAY mice. Except for the study